RESPONSE

The Examiner has raised a variety of rejections based on § 112, and rejections under § 102 based on the asserted content of various prior art references. Each such rejection is addressed in turn.

1. The recitation of the term "locus" in claim 10 is removed—however, the applicant submits that replacement of the claims would aid clarity and would be entirely proper for the following reasons: The phrase "locus" is defined inter alia at the U.S. Government publication for the OMIM – Online Mendelian Inheritance in Man – by the U.S. Department of Energy as follows:

- The gene map locus describes where a gene can be found on a chromosome. For the gene locus 6p21.3, 6 is the chromosome number. p indicates the short arm of the chromosome, and 21.3 is the number assigned to a particular band on a chromosome. The gene map locus links to the OMIM's Gene Map.

http://www.ornl.gov/sci/technosources/Human_Genome/posters/chromosomal/omim.shtml 9/24/08 page 11 of 12.

See also the following references enclosed with this paper:

1) "Stepwise activation of the immunoglobulin μ heavy chain gene locus" Chowdhury et al., *The EMBO Journal*, v. 20:22, pp. 6394-6403, 2001.

2) "Immunoglobulin β Signaling Regulates Locus Accessibility for Ordered Immunoglobulin Gene Rearrangements," Maki, et al., *J. Exp. Med.*, The Rockefeller University Press, 191:9 1333-1340, April 17, 2000.

2. The phrase pseudo gene is proper--As noted in the previous responses, the phrase "pseudo" in connection with the "pseudo v genes" is completely consistent with the use of the term in the prior art. The examples are numerous and readily ascertainable in the prior art. Examples of the accepted usage of the term "pseudogene" include:

Polymorphism of the functional immunoglobulin variable region genes in the chicken by exchange of sequence with donor pseudogenes. Eur J Immunol. 1993 Oct;23(10):2448-53; Benatar T, Ratcliffe MJ.

Germ line maintenance of the pseudogene donor pool for somatic immunoglobulin gene conversion in chickens. McCormack WT, Hurley EA, Thompson CB Mol Cell Biol. 1993 Feb;13(2):821-30.

Evolution of immunoglobulin V_H pseudogenes in chickens. Mol Biol Evol. 1995 Jan;12(1):94-102. Ota T, Nei M.

The Ota and McCormack references are enclosed. The definite meaning and scope of the term "pseudogene" does not require that a differential be created between a "gene" and "pseudogene" or that a defined transition point between those two terms can be shown to exist. The phrase "pseudogene" is entitled to the ordinary interpretation as reflected in the specification and claims and as informed by usage in the art as is reflected in the references. Moreover, as the references clearly demonstrate, there are no other terms that appropriately describe the V_H genes other than the "pseudogene" term that is actually used by those in the art, and that term is adopted here. Clearly,

particularly in the context of the immunoglobulin gene, the term "pseudogene" is sufficiently clear and is used in the art to define the variable region pseudogenes of the avian immunoglobulin gene. Applicants submit that, on this record, the rejection is traversed.

3. The term "conversion" is clear and definite in scope—The term conversion in claim 10 is clear because the language plainly indicates that it is the immunoglobulin gene in the genome of the chimeric chicken the gene undergoes "conversion." Gene conversion is a well-recognized form of immunoglobulin gene rearrangement that is indisputably known to those of ordinary skill.

4. Claim 16 is amended for clarity—The term "rearrangement" was previously removed and the phrase is simply intended to clarify that the method of functional immunoglobulin gene conversion in the animal as claimed is the specific mechanism of class switching. Applicants note that the phrase "rearrangement" is removed from claim 16.

5. Section 102—Rapp et al.

With respect to the cited prior art references, none of these disclose the application as claimed. The Rapp U.S. Patent Publication No. 2002/0108132-A12002 reference does not anticipate the pending claims. As previously noted, the present claims require that the genes undergo functional immunoglobulin gene rearrangement.

Rapp is directed to expression of a monoclonal antibody in a chicken and does not feature an animal having a population of B lymphocytes containing human immunoglobulin gene locus. The main presence of a switch region does not demonstrate diversity of the antibody repertoire. It is well known that the ability to express an I_gG repertoire requires expression at I_gM and rearrangement of the I_g gene—Rapp shows no such phenomenon and it would be contrary to Rapp's stated purpose of expressing the monoclonal.

The examiner cites Example 11 of Buelow as prior art. However, this is fictitious data - BACs encompassing the chicken heavy chain locus do not exist. Similarly, Example 13 cites an "agammaglobulinemic " chicken. However, the cited chicken is not agammaglobulinemic - it is hypo-gammaglobulinemic (because they were selected for low concentrations of IgY) and only marginally so. The immune system of these birds is entirely normal. Hence, the "teachings" of Buelow are incorrect.

The Examiner citation to Buelow refers to retroviral transfection that is clearly incapable of transferring an immunoglobulin locus into a recipient embryo. Because the retroviral transfection methodology is known to be size limited (usually less than 10-15kb), no retroviral technology at the time of filing of the Buelow reference could produce human immunoglobulins to meet the threshold of enablement under §112 to constitute an operative reference under 35 U.S.C. § 102 or § 103.

With respect to the rejection over Singh, U.S. Patent Publication No. 2002/0028488, as noted previously, the Singh publication is a farce. Singh et al. merely copied the United States patent of another that relates only to expression of human

immunoglobulins in transgenic mice. Singh et al. is conspicuously non-enabling for the subject matter of the present claims because the specific gene modifications and restriction sites, etc., and essentially all functional portions of the Singh et al. publication are directed to the mouse genome, not the chicken genome. Therefore, the teachings of Singh et al. cannot reach the invention here.

Finally, as noted previously, a chimeric chicken carrying a transgene was first made in 2004—three years after the Buelow application was filed. The novelty of making a transgenic chimera was recognized by the patent office in the grant of USP 7,145,057. Clearly, making a chimeric chicken as claimed was not within the ability of an ordinary artisan.

Therefore, none of the prior art references anticipates or renders obvious the present claims.

The Commissioner is also authorized to charge $525.00 for the three-month extension fee to Orrick Herrington & Sutcliffe's Deposit Account No. **150665** and charge any fees required by the filing of this papers, and to credit any overpayment to Orrick Herrington & Sutcliffe's Deposit Account No. **150665.**

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLP

Dated: September 25, 2008

By: _____
Kurt T. Mulville
Reg. No. 37,194

Orrick, Herrington & Sutcliffe LLP
4 Park Plaza, Suite 1600
Irvine, CA 92614-2558
Tel. 949-567-6700
Fax: 949-567-6710